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Enantioselective conjugate addition of diethylzinc using catalytic silver(I) diaminocarbenes and Cu(OTf)$_2$

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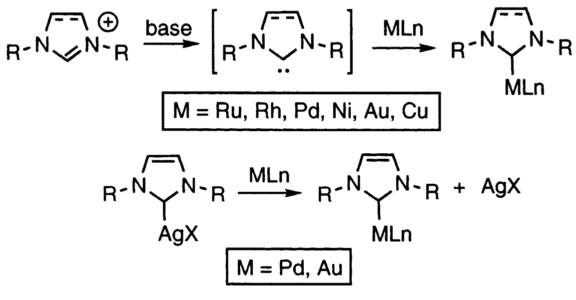
Abstract—Chiral silver(I) diaminocarbenes act as efficient carbene transfer agents to copper salts. The catalytic species, active in the conjugate addition of diethylzinc to cyclohexenone, is prepared easily at room temperature in various solvents by simply mixing the silver carbene and Cu(OTf)$_2$. This method avoids the use of strong bases and polar solvents to generate the carbene. The chiral diaminocarbene–copper catalyst, formed in situ, shows a strong accelerating effect and gives enantiomeric excesses up to 23%. © 2001 Elsevier Science Ltd. All rights reserved.

N-Heterocyclic carbenes have recently emerged as an important family of ligands with electronic characteristics similar to those of the phosphines.[1] The use of imidazol-2-ylidene, thiazol-2-ylidene and imidazolidin-2-ylidene metal complexes rapidly showed an increased interest since it was demonstrated that they are efficient catalysts in important chemical transformations, such as Ni and Pd carbon–carbon coupling reactions, CO-ethylene copolymerisations, Ru-catalysed olefins metathesis and Rh catalyzed hydrosilylations. Initially, the widespread use of catalysts with carbene ligands was limited due to their relatively difficult preparation. The first syntheses have utilized the free carbenes, obtained by deprotonation of the corresponding azolium salts, which are extremely air and moisture sensitive. Recent investigations have demonstrated that the free carbenes can be generated and directly trapped in situ (Scheme 1).[2]

In 1998, Wang and Lin showed that a silver benzimidazol-2-ylidene complex could be easily obtained by treatment of the corresponding azolium salt with Ag$_2$O.[3] Moreover, this silver carbene complex acts as an effective carbene transfer agent for the synthesis of palladium or gold carbene complexes (Scheme 1). This methodology was applied recently with success by McGuinness and Cavell towards the synthesis of palladium imidazol-2-ylidene complexes which are efficient catalysts for C–C coupling reactions.[4] Syntheses and structures of *N*-functionalised silver(I) carbene complexes derived from imidazolium salts were also reported by Danopoulos et al. in 2000.[5]

Such an approach is mild and compatible with the presence of acidic protons in chains of the azolium salts and we recently reported that chiral silver(I) diaminocarbenes can also be easily obtained from the less acidic imidazolinium precursors and Ag$_2$O.[6] This provided a very convenient method for the formation of chiral carbene complexes by overcoming many of the difficulties arising from the use of strong bases.

Copper(I) carbene complexes derived from imidazolium salts were synthesized and characterized for the first time by Arduengo in 1993 by reaction of the free carbene with copper triflate.[7] In 2001, Woodward et al. reported the first ligand accelerated catalysis with an



Scheme 1. Preparation of diaminocarbene–metal complexes.

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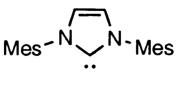
Arduengo-type carbene in copper-catalyzed conjugate addition.[8] In their study, the diaminocarbene ligand **1** was not isolated but generated by deprotonation of the precursor imidazolium salt by Bu^{t}OK in THF. This THF solution was then added to a solution of $Cu(OTf)_2$ to form the pre-catalytic copper species.



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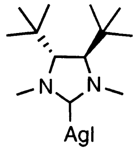

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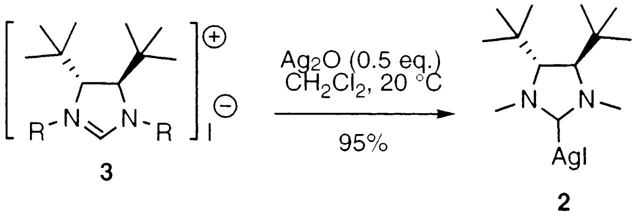
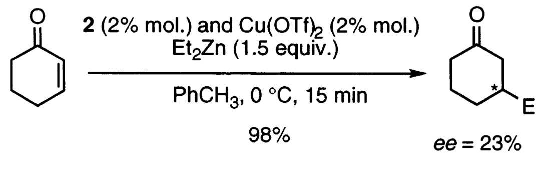
Synthesis and use of chiral diaminocarbene complexes remains an important challenge for organic chemists and only a few catalysts have been reported.[9] Herein, we report our first results on the enantioselective conjugate addition of diethylzinc to cyclohexenone using the chiral silver(I) diaminocarbene **2** and $Cu(OTf)_2$. In our studies, **2** was obtained by reaction of the corresponding chiral imidazolinium salt **3** and Ag_2O (0.5 equiv.) in CH_2Cl_2 (Scheme 2) as previously reported.[6] This compound is a crystalline solid that can be isolated and easily handled.

In our first experiment, the Ag(I) carbene **2** (2%) was dissolved in toluene at room temperature and $Cu(OTf)_2$ (2%) was added. A white precipitate appeared after stirring for 5 min. The mixture was cooled to 0°C and diethylzinc (1.5 equiv.) was added followed by cyclohexenone. The conjugate adduct was obtained in less than 30 min and a moderate e.e. of 23% was measured on the isolated compound (Scheme 3).

The strong ligand accelerated catalysis (LAC) effect of the silver carbene in the presence of $Cu(OTf)_2$ was examined by comparison with the same experiment, at 0°C in $PhCH_3$, with $Cu(OTf)_2$ alone (Fig. 1, graph B). The reaction was slower and only a 22% conversion was achieved after 15 min. We also checked that the diaminocarbene did not catalyze the reaction in the absence of $Cu(OTf)_2$ (Fig. 1, graph A). In this case, the rate of the reaction was still lower than with copper triflate alone (11% conversion after 15 min).[10]



Scheme 2. Synthesis of chiral silver(I) diaminocarbenes from imidazolinium salts.



Scheme 3. Conjugate addition using **2** and $Cu(OTf)_2$.

The solvent-dependency of this reaction was studied and the results are presented in Table 1. The accelerating effect of the diaminocarbene **2** was also very important in hexane or diethylether and the rates of the reaction are similar to these observed in toluene (Table 1, entries 1–3). Nevertheless, the conjugate addition was significantly slower in CH_2Cl_2 since only 62% of conversion was achieved after 1 h at 0°C (entry 4). A dramatic decreasing of the reactivity was also observed in THF (28% of conversion after 1 h) (entry 5). The best e.e. (23%) was obtained in $PhCH_3$ while Et_2O and hexane gave similar excesses (15–16%) and no enantioselectivity was observed in CH_2Cl_2 and THF. The reaction in toluene was still fast until a temperature of −40°C but was slowed down at −78°C (entries 6–8). The more surprising result was the decrease in the e.e. when the temperature was lowered (entries 1 and 6–8). An e.e of only 4% was measured on the adduct obtained at −78°C in $PhCH_3$, compared to 23% at 0°C. The major enantiomer in all these experiments was identical. Its absolute configuration (*S*) was determined by ^{13}C NMR after formation of the aminal with (*R*,*R*)-1,2-diphenyl-1,2-diaminoethane.[11]

In conclusion, the chiral silver(I) diaminocarbene **2** acts as efficient carbene transfer agent to copper(II) triflate. The catalytic species, active in the conjugate addition of diethylzinc to cyclohexenone, is prepared easily at room temperature and in various solvents. This method avoids the use of strong bases and polar solvents to generate the carbene. The chiral diaminocarbene–copper catalyst, formed in situ, shows a strong accelerating effect and gives moderate enantiomeric excesses up to 23%.

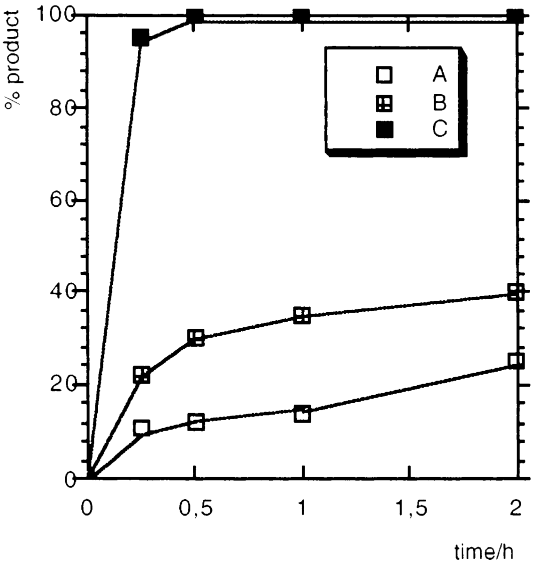


Figure 1. Ligand accelerated catalysis with the silver(I) diaminocarbene **2** and copper(II) triflate in $PhCH_3$ at 0°C. Graph A: 2% diaminocarbene **2**. Graph B: 2% $Cu(OTf)_2$. Graph C: 2% diaminocarbene **2**+2% $Cu(OTf)_2$. The conversions were determined by GC.

Table 1. Influence of the temperature and solvent

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	E.e (%)[b]
1[c]	$PhCH_3$	0	0.25	98	23
2	Hexane	0	0.25	99	16
3	Et_2O	0	0.25	95	15
4	CH_2Cl_2	0	0.25 (1)	37 (62)	0
5	THF	0	0.25 (1)	12 (28)	0
6	$PhCH_3$	−20	1	99	16
7	$PhCH_3$	−40	1	98	10
8	$PhCH_3$	−78	1	78	4

Typical procedure: A mixture of silver(I) diaminocarbene **2** (2% mol, 0.025 mmol) and $Cu(OTf)_2$ (2% mol, 0.025 mmol) in the appropriate solvent (5 ml) was stirred for 5 min at 20°C. To this suspension was added Et_2Zn (1.1 M in hexane, 1.87 mmol). The mixture was brought to the appropriate temperature and cyclohexenone was added. The reaction was hydrolyzed with HCl 5N, extracted with ether, dried on $MgSO_4$ and concentrated. The crude was purified by silica-gel chromatography (pentane/Et_2O, 9:1).

[a] Conversion determined by GC after quenching with HCl.

[b] Determined by chiral GC (Lipodex E, 100°C).

[c] The same experiment performed with 4% mol of **2** and 2% mol of $Cu(OTf)_2$ led to identical results regarding the reaction rate and to a similar *ee* of 20%.

Acknowledgements

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